Relationship of lipoprotein-associated phospholipase A2(Lp-PLA2) and periprocedural myocardial injury in patients undergoing elective percutaneous coronary intervention

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) is one of the dominant methods for revascularization in patients with coronary heart disease (CHD). However, periprocedural myocardial injury (PMI) is a frequent complication following PCI and is known to be a predictor of postprocedural cardiovascular morbidity and mortality. Although several studies try to identify serum markers to predict the PMI, there is a little information about the role of lipoprotein-associated phospholipase A2 (Lp-PLA2) as a predictor of PMI. Therefore, we aimed to investigate the relationship of Lp-PLA2 levels and PMI in patients undergoing elective PCI.
Methods: This study included 265 consecutive patients with normal preprocedural cardiac troponin T (cTNT) who received elective PCI. The samples for cTNT were collected at 8, 16, and 24 h after PCI to assess perioperative myocardial injury. The Lp-PLA2 and other serum lipid parameters were measured after 12 fasting hours before PCI.
Results: The data suggested that the patients with preprocedural high Lp-PLA2 were strongly and independently correlated with the risk of PMI. Pearson correlation analysis showed that preprocedural Lp-PLA2 was significantly positively correlated with postprocedural cTnT elevation ($r = 0.694$, $p < 0.05$). Binary logistic regression analysis was used to analyze the risk factors of PMI, we found that Lp-PLA2 was independent risk factor for postprocedural cTnT elevation. The area under Receiver Operating Characteristic curve of Lp-PLA2 was 0.757 (*95%CI* 0.692 ~ 0.821, $p < 0.001$), the best cut-off point was 185 ng/ml, sensitivity and specificity were 65.33% and 76.32%.
Conclusion: Our study demonstrated that preprocedural Lp-PLA2 was associated with postprocedural cTnT elevation and was the independent risk factor of PMI.

1. Introduction

PCI has become one of the most important methods to revascularize the coronary. However, periprocedural complications and adverse outcomes still have increased despite the benefits of technical advances and effective medical therapy. Studies have shown that 32% of patients had evidence of periprocedural myocardial injury that assessed by cardiac magnetic resonance [1]. Recently, the fourth edition of the universal definition of myocardial infarction has been published, and PMI is clearly definited. Perioperative myocardial injury is arbitrarily defined by increases of cTn values [>99th percentile upper reference limit(URL)] in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values > 20% of the baseline value when it is above the 99th percentile URL but it is stable or falling, and the post-procedure cTn must rise > 20% to an absolute value less than five times the 99th percentile URL [2]. Multiple clinical trials have established that PMI is an independent predictor of adverse clinical outcomes, and contributes compelling evidence that it may be a clinically meaningful complication of PCI [3]. Several serum markers are found to be correlated with the incidence of PMI, yet the specific indicators are not been confirmed [4].

Lp-PLA2 is a novel inflammatory factor which associated with CHD [5]. Recent studies have shown that Lp-PLA2 is significantly increased in patients with acute coronary syndromes, and it is reported to be related with the stability of atherosclerotic plaques [6]. Our previous researches have shown that Lp-PLA2 may be a potential candidate for predicting cardiovascular events. However,

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the relationship between Lp-PLA2 levels and PMI has not been reported, and little is known about whether patients with higher levels of Lp-PLA2 have higher risk of PMI. Therefore, the objective of this paper was to elucidate the connection between preprocedural Lp-PLA2 levels and PMI in patients undergoing elective PCI.

2. Materials and methods

2.1. Patients and study design

This study was enrolled 265 consecutive patients with a diagnosis of coronary heart disease who underwent PCI between June 2015 and August 2018 at Department of Cardiology,Yixing people's hospital. This sample size was calculated with the MedSci software (MedSci Sample Size tools, MSST). CHD patients were eligible for inclusion if they exhibited: (1) stable angina, or unstable angina and received elective PCI surgery, and (2) normal pre-procedural cTnT level and creatinine-MB fraction (CK-MB). The major exclusion criteria were: (1) ST segment elevation or non-ST segment elevation acute myocardial infarctions, (2) died after PCI or angiography failed, (3) incomplete data, (4) PCI-related myocardial infarctions ,and (5) other severe diseases such as acute cerebral hemorrhage, severe liver and kidney diseases,autoimmune diseases. The diagnosis of PMI was based on the elevation of cTNT. The post-procedure cTnT must be a rise of cTnT values > 20% of the baseline value and within 5 times of the baseline value. This study was performed in accordance with the 1964 Declaration of Helsinki and was approved by Human Ethics Committees of Yixing People's Hospital.

2.2. Percutaneous coronary intervention

The indications for PCI were based on recommendations from the ACC/AHA, and all patients were operated by experienced interventional cardiologists. Patients were treated with aspirin (100 mg/day) and clopidogrel (300 mg) at least 4 h before PCI. All patients accepted heparin 5000U or 70U/kg before surgery, and 2000-3000U was added when the procedure lasted>1 h. All patients continuously received aspirin and clopidogrel daily after PCI. Glycoprotein IIb/IIIa inhibitors were used at the surgeon's discretion. Stents were implanted if the stenosis was>70% According to the angiography. FFR and IVUS were used to determine whether stents should be implanted in the borderline lesions. SYNTAX score was used to evaluate the severity of coronary heart disease. Lesion characteristics were measured by using the QCA method(Siemens Imaging Analysis System).

2.3. Electrocardiography(ECG)

In all patients, a 12-lead ECG was recorded before, immediately after PCI, and in the case of the occurrence of symptoms that were interpreted as a postprocedural ischemic event. All patients received continuous ECG monitoring using wireless technology after PCI during hospitalization.

2.4. Laboratory measurements

Samples for serum lipid parameters were collected after 12–14 fasting hours immediately preprocedurally and measured via Clinical Central Laboratory of Yixing People's Hospital. The samples for cTNT were collected at 8, 16, and 24 h postprocedurally. The cTNT levels were measured by chemiluminescence(ACCESS2 and reagents, Beckman Kurt, USA). The plasma Lp-PLA2 content was determined by colorimetric method. The reagents were supplied by the Norman Company of Nanjing. The hs-CRP levels were detected by kits that provided by Beijing Company of Science and Technology Biotechnology Co., Ltd.

2.5. Statistics

All data were statistically analyzed by SPSS software (SPSS 16 for Windows, SPSS Inc., Chicago, Illinois). The data were expressed as mean ± SD for the continuous and as percentages for the discrete variables. The independent samples t test or Mann Whitney U test was used to compare the continuous variables between two groups. The chi-square test was employed for the statistical analysis of the categorical variables. Binary logistic regression analyses were performed to determine the relationship of LP-PLA2 with the occurrence of postprocedural cTnT elevations. Odds ratios and 95% confidence intervals (CI) were presented with two-tailed p values. P values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

265 patients who underwent selective PCI with a diagnosis of coronary heart disease were enrolled in this study. There were 75 patients with elevated cTnT after PCI, and 190 patients without elevated cTnT. The clinical characteristics of patients with and without PMI were summarized in Table 1. In our study, we found that Lp(a), SYNTAX score and Lp-PLA2 were significantly different between the two groups. Subjects with PMI had higher Lp(a) and Lp-PLA2 levels. The SYNTAX score was also higher in patients with PMI. There was no difference in the use of Medications, age, Gender, hypertension, diabetes, smoking, Previous PCI, unstable AP, TC, HDL-C, LDL-C, ApoA1, ApoB, hs-CRP, creatinine, number of stents, total stent length, stent release pressure and Quantitative Coronary Angiography.

3.2. Correlation analysis of Lp-PLA2 levels with postprocedural cTnT elevation

Independent sample t test showed that the level of Lp-PLA2 in patients with elevated cTNT after PCI was significantly higher than that in patients with normal cTNT after PCI (155.12 ± 91.69 vs 247.25 ± 119.54, $p < 0.001$) (Table 1). Pearson correlation analysis showed that preprocedural Lp-PLA2 was significantly positively correlated with postprocedural cTnT elevation ($r = 0.694$, $p < 0.05$) (Fig. 1).

3.3. Factors independently associated with PMI

Binary logistic regression analysis indicated that hs-CRP, SYNTAX score and Lp-PLA2 were risk factors for perioperative myocardial injury in patients undergoing PCI. ROC curve was used to predict the incidence of PMI (Table 2). When adjusted for age, gender, history of hypertension, history of diabetes, smoking and previous PCI, there was no significance with hs-CRP in predicting PMI (Table 3). We found that The area under ROC curve of hs-CRP was 0.572, however there was no predictive value. The area under ROC curve of SYNTAX scores was 0.678 ($95\%CI$ 0.609 ~ 0.747, $p < 0.001$). The area under ROC curve of Lp-PLA2 was 0.757 ($95\%CI$ 0.692 ~ 0.821, $p < 0.001$), the best cut-off point was 185 ng/ml, sensitivity and specificity for diagnosis of PMI were 65.33% and 76.32%, respectively (Table 4, Fig. 2).

Table 1
Baseline Clinical Characteristics.

Characteristics	Periprocedural myocardial injury		P Value
	No (n = 190)	Yes (n = 75)	
Age,yrs	65.73 ± 8.27	67.56 ± 9.52	0.123
Gender,male(%)	107 (56.32%)	47 (62.67%)	0.345
Hypertension(%)	168 (88.42%)	60 (80.00%)	0.075
Diabetes(%)	88 (46.32%)	40 (53.33%)	0.303
Smoking(%)	79 (41.58%)	27 (36.00%)	0.404
Previous PCI(%)	45 (23.68%)	11 (14.67%)	0.105
Unstable angina pectoris(%)	9(4.74%)	2(2.67%)	0.447
Medications(%)			
Aspirin/clopidogrel	182 (100.00%)	72 (100.00%)	0.938
Beta-blockers	157 (82.63%)	64 (85.33%)	0.594
Statin	174 (91.57%)	69 (92.00%)	0.911
ACEI/ARB	142 (74.73%)	60 (80.00%)	0.365
Lipid Parameters			
TC(mmol/L)	4.06 ± 0.94	4.28 ± 1.03	0.09
HDL-C(mmol/L)	1.08 ± 0.43	1.07 ± 0.19	0.908
LDL-C(mmol/L)	2.34 ± 0.74	2.31 ± 0.66	0.796
ApoA1(g/L)	1.26 ± 0.18	1.31 ± 0.22	0.089
ApoB(g/L)	0.84 ± 0.25	0.85 ± 0.22	0.906
Lp(a)(mg/L)	235.76 ± 243.81	323.57 ± 348.12	0.048
hs-CRP(mg/L)	7.95 ± 11.31	11.42 ± 17.11	0.109
Creatinine(umol/L)	73.13 ± 18.74	74.95 ± 25.88	0.526
Characteristics during PCI			
SYNTAX score	20.61 ± 6.47	25.06 ± 6.77	<0.001
Number of Stents(n)	1.66 ± 0.87	1.73 ± 0.93	0.564
Total stent length(mm)	46.81 ± 27.83	46.88 ± 26.83	0.986
Stent release pressure(atm)	9.85 ± 2.68	10.02 ± 3.11	0.65
Quantitative Coronary Angiography MLD(mm)	1.37 ± 0.22	1.36 ± 0.28	0.717
DS(%)	62.88 ± 5.57	63.52 ± 4.89	0.388
Lp-PLA2(ng/mL)	155.12 ± 91.69	247.25 ± 119.54	<0.001

In our study, we found that Lp(a), SYNTAX score and Lp-PLA2 were significantly different between the two groups. Subjects with PMI had higher Lp(a) and Lp-PLA2 levels. The SYNTAX score was also higher in patients with PMI. There was no difference in the use of Medications, age, Gender, hypertension, diabetes, smoking, Previous PCI, unstable AP, TC, HDL-C, LDL-C, ApoA1, ApoB, hs-CRP, creatinine, number of stents, total stent length, stent release pressure and Quantitative Coronary Angiography.
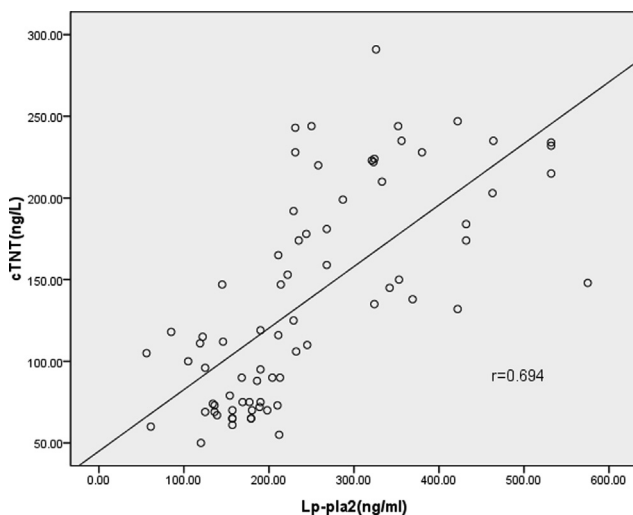

Fig. 1. Correlation between Lp-PLA2 and postprocedural cTnT. Pearson correlation analysis showed that preprocedural Lp-PLA2 was significantly positively correlated with postprocedural cTnT elevation ($r = 0.694$, $p < 0.05$).

4. Discussion

The present study demonstrates that the relationship of preprocedural Lp-PLA2 levels with PMI in patients undergoing PCI. The main finding of this study was that preprocedural Lp-PLA2 levels was associated with an increased risk of periprocedural myocardial injury, and preprocedural Lp-PLA2 levels may be an useful serological indicators for predicting PMI. PCI is one of most important procedures to revascularize the lesion vessel. It can significantly improve the symptoms of myocardial ischemia and reduce the incidence of vascular events in patients with coronary heart disease. Despite the known safety and minimally invasive nature of the procedure, it may result in cardiac injury in about one-third of patients undergoing elective PCI and influence patients' outcomes [7].

American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines have also focused on PMI and recommended the check of cardiac biomarkers following PCI for outcome assessment [2]. The diagnosis of PMI was based on the elevation of cTNT. The post-procedure cTnT must be a rise of cTnT values > 20% of the baseline value and within 5 times of the baseline value [8]. Commonly, PMI occurs because of embolization of thrombotic plaque, platelet aggregation, thrombosis formation, coronary artery vasospasm, oxidative stress, and inflammation [9]. The clinical significance of elevation of cardiac biomarkers following PCI has been described by large studies. A *meta*-analysis of 10 randomized, 48,022 patients who underwent PCI have been included in the study, it shows that even a small increase in CK-MB levels after PCI is associated with significantly higher risk of late mortality. Monitoring cardiac enzymes after PCI may help predict the long term clinical outcome [10]. Another *meta*-analysis of 15,581 patients included showed troponin elevation after elective PCI provides increased mortality (4.4% vs. 3.3%, P = 0.001; OR 1.35) [11]. Occurrence of major adverse cardiovascular event (MACE) were significantly lower in patients with coronary chronic total occlusion (CTO) successfully treated without PMI occurrence compared to those with PMI according to a study of long-term clinical outcome in patients undergoing PCI of CTO [12]. Other studies have found that PMI may not be associated with clinical prognosis in patients undergoing PCI of CTO [13–14]. Despite the controversy, PMI is still considered as an important indicator of cardiovascular events. It underlines the importance of risk stratifying prior to the PCI to identify the patients that most likely to develop PMI. Clinical outcomes would be expected to improve if PMI incidence can be reduced.

Studies showed that PMI was affected by many factors, such as clinical risk factors, coronary artery disease related risk factors and interventional therapy related risk factors [15–16]. Considering the above factors, the stability of plaque is the most critical factor for PMI. The stability of plaque is mainly related to the morphology and inflammation of plaque. The methods of OCT and IVUS are used to detect the plaque morphology, which is relatively expensive and invasive, with high technical requirements and is not easy to be popularized in clinical practice [17]. Now, some serological indicators predicting PMI in patients undergoing elective PCI have been studied. Wang and his colleagues found that free fatty acids may be a predictor of perioperative myocardial damage after coronary intervention [18]. Another study found that the ratio of neutrophils to lymphocytes in patients undergoing selective percutaneous coronary intervention was closely related to PMI [19]. Other factors have been reported to be associated with PMI, such as blood lipids and C-reactive protein [4].

Our previous researches have shown that Levels of Lp-PLA2 increased in PMI patients, suggesting that Lp-PLA2 may be associated with PMI. Lp-PLA2 belongs to the phospholipase superfamily. It is a calcium-independent secretory protein with a molecular weight of 45 KDa. There are two main forms of Lp-PLA2 in human body, one is sLp-PLA2 in circulating blood, the other is Lp-PLA2 in plaque [20–21]. Lp-PLA2 is produced by macrophages in atherosclerotic plaques and converted into sLp-PLA2 into blood. It binds to lipoprotein particles containing apolipoprotein B. About

Table 2
Risk factors of PMI.

Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% CI.for EXP(B)	
							Lower	Upper
LDL-C	−0.402	0.283	2.014	1	0.156	0.669	0.384	1.166
ApoB	0.767	0.842	0.829	1	0.362	2.152	0.413	11.208
Lp(a)	0.001	0.001	2.173	1	0.140	1.001	1.000	1.002
hs-CRP	0.025	0.012	4.166	1	0.041	1.025	1.001	1.050
SYNTAX scores	0.101	0.025	16.868	1	<0.001	1.106	1.054	1.161
Number of Stents	0.592	0.463	1.636	1	0.201	1.807	0.730	4.476
Total stent length	−0.017	0.015	1.319	1	0.251	0.983	0.954	1.012
Stent release pressure	−0.005	0.057	0.008	1	0.931	0.995	0.890	1.113
Lp-PLA2 ≥ 185 ng/mL	2.072	0.339	37.409	1	<0.001	7.937	4.087	15.415

Binary logistic regression analysis indicated that hs-CRP, SYNTAX score and Lp-PLA2 were risk factors for perioperative myocardial injury in patients undergoing PCI.

Table 3
Adjusted risk factors of PMI.

Variable	B	S.E.	Wald	df	Sig.	Adjusted Exp(B)	95.0% CI.for Adjusted EXP(B)	
							Lower	Upper
hs-CRP	0.018	0.013	2.148	1	0.143	1.019	0.994	1.014
SYNTAX scores	0.110	0.025	18.495	1	<0.001	1.116	1.061	1.173
Lp-PLA2 ≥ 185 ng/mL	2.050	0.346	35.095	1	<0.001	7.766	3.942	15.300

We adjusted for age, gender, history of hypertension, history of diabetes, smoking and previous PCI, there was no significance with hs-CRP in predicting PMI. While SYNTAX scores and Lp-PLA2 ≥ 185 were risk factors for perioperative myocardial injury in patients undergoing PCI.

Table 4
ROC curve of hs-CRP, SYNTAX scores and Lp-PLA2.

Variable	Area	Std. Error	Asymptotic sig.	Asymptotic 95% confidence Interval	
				Lower bound	Upper bound
SYNTAX scores	0.678	0.035	<0.001	0.609	0.747
Lp-PLA2	0.757	0.033	<0.001	0.693	0.821

The area under ROC curve of SYNTAX scores was 0.678 (*95%CI* 0.609 ~ 0.747, *p* < 0.001). The area under ROC curve of Lp-PLA2 was 0.757 (*95%CI* 0.692 ~ 0.821, *p* < 0.001), the best cut-off point was 185 ng/ml, sensitivity and specificity for diagnosis of PMI were 65.33% and 76.32%, respectively.
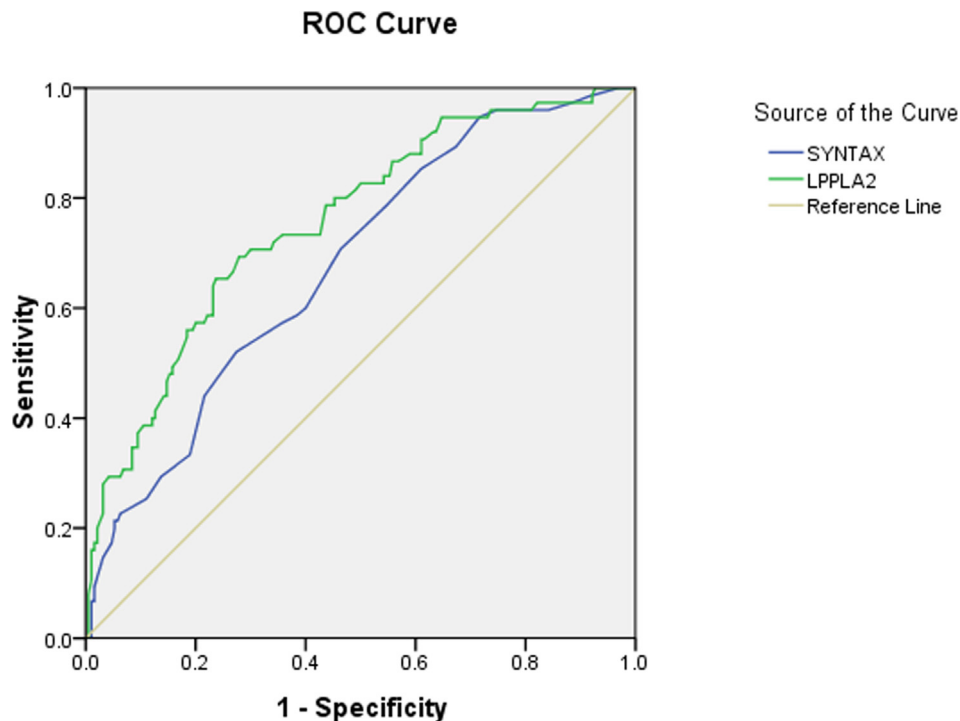

Fig. 2. The area under ROC curve of Lp-PLA2 was 0.757 (*95%CI* 0.692 ~ 0.821, *p* < 0.001), the best cut-off point was 185 ng/ml, sensitivity and specificity for diagnosis of PMI were 65.33% and 76.32%, respectively.

70% of sLP-PLA2 binds to low density lipoprotein cholesterol (LDL) to produce hemolytic lecithin and oxidized free fatty acids. The remaining binds to high density lipoprotein(HDL) or very low density lipoprotein cholesterol (VLDL) [22]. In atherosclerotic plaque, Lp-PLA2 hydrolysis and oxidation modified low density lipoprotein-cholesterol (ox-LDL) particles produce the above metabolites, which promote endothelial dysfunction, necrosis and apoptosis through inflammatory chain reaction, leading to the progression of atherosclerosis and plaque instability [23]. Lp-PLA2 can highly specifically indicate the presence of inflammation in plaques, so measuring the level of Lp-PLA2 can accurately reflect the stability of plaques, and its predictability to vulnerable plaques is better than traditional non-specific inflammatory factors such as hs-CRP and IL-6 [24].

Therefore, the objective of this paper was to elucidate the connection between preprocedural Lp-PLA2 levels and PMI in patients undergoing elective PCI. This study included 265 consecutive patients with normal preprocedural cardiac troponin T(cTNT) who received elective PCI. The data suggested that the patients with preprocedural high Lp-PLA2 were strongly and independently correlated with the risk of PMI. Pearson correlation analysis showed that preprocedural Lp-PLA2 was significantly positively correlated with postprocedural cTnT elevation(R = 0.558, $p < 0.05$). Binary logistic regression analysis was used to analyze the risk factors of PMI, we found that Lp-PLA2 is independent risk factor for postprocedural cTnT elevation.The area under ROC curve of Lp-PLA2 was 0.757 ($95\%CI$ 0.692 ~ 0.821, $p < 0.001$), the best cut-off point was 185 ng/ml, sensitivity and specificity for diagnosis of PMI were 65.33% and 76.32%, respectively.

The results show that Lp-PLA2 can be used as an independent predictor of risk assessment of PMI. Because PMI may be related to many clinical, anatomical and procedural confounding factors including characteristics of culprit lesion and complications during PCI, it will be important to introduce these data in different groups and present bias-adjusted results for future studies.There may be some deficiencies in this study. Firstly, because it is not a large sample multi-center prospective study, the results may be biased. Secondly, there are individual differences in interventional therapy and differences in the operation process. We will further expand the sample size to verify this conclusion, and further explore whether Lp-PLA2 can be used as a target for intervention, so as to reduce the incidence of PMI.

Acknowledgements

Human Subjects/Informed Consent Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest.

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100541.

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